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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,140	BRINES ET AL.	
	Examiner	Art Unit	
	CHERIE M. WOODWARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-46,53 and 54* is/are pending in the application.

4a) Of the above claim(s) *1-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-46, 53, 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicant's response and amendments to the specification and claims, filed 28 September 2007 is acknowledged and entered. Claims 1-5, 8-46 are pending. Claims 6-7 and 47-52 have been cancelled by Applicant. New claims 53-54 have been added. Claims 1-5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 19 December 2006. Claims 8-46 and 53-54 are under examination.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 28 September 2007 has been considered. It is noted that the IDS is 27 pages long and contained multiple pages of duplicative references. This duplicative material has been lined through and only the first disclosure of a reference has been considered. Additionally, two of the WO references have been lined through because they are not in English and no English translation was provided. These references will be considered when translations are provided. It is also noted that copies of several references were submitted along with copies of the documents listed in the IDS, but these references were not actually listed anywhere in the IDS. Because these references were not listed in the IDS, they have not been considered. A signed copy of the IDS is attached hereto.

Response to Arguments

Claim Objections/Rejections Withdrawn

3. The objection to claim 39 is withdrawn in light of Applicant's amendment.

4. The objection to the trademarks in the specification is withdrawn in light of Applicant's amendment to the specification.

5. The objection to the disclosure because of the blank space on page 115, paragraph 323, lines 3 to 4, is withdrawn in light of Applicant's deletion of the blank space.

6. The rejection of claims 8, 43, and 44 under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendments.

7. The rejection of claims 11-12 and 17-42 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, are withdrawn.

8. The rejection of claims 8-46 under 35 U.S.C. 103(a) as being unpatentable over Brines et al., PNAS USA, 2000 Sept 12; 97(19):10526-10531, in view of Lin et al., (US Patent 5,621,080, 15 April 1997) and Satake *et al.* (Biochimica et Biophysica Acta. 1990;1038:125-129), is withdrawn.

9. The rejection of claims 8-11, 12-16, 19-20, 28-29, and 43-46 under 35 U.S.C. 102(b) as being anticipated by Brines et al., (PNAS USA, 2000 Sept 12; 97(19):10526-10531), is withdrawn.

Claim Objections/Rejections Maintained

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 8-46 remain rejected and new claims 53 and 54 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement. For purposes of clarity and in order to better respond to Applicant's arguments, the reply to Applicant's response for the scope of enablement rejection has been split in two parts, the first part directed to the generic claims and the second part directed to the claims that specifically recite EPO or modified EPO. Additionally, due to the length of Applicant's arguments, each argument will be addressed and responded to point-by-point.

(Part I)

12. Claims 8-10, 13-16, 43-46 remain rejected and new claim 54 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling in the art for a method of treating inflammation in a mammal comprising administering recombinant Epoetin Alpha in an isotonic sodium chloride solution with IFN-β, does not reasonably provide enablement for a method of treating inflammation in a mammal comprising administering a generic tissue protective cytokine, and a pharmaceutically acceptable carrier and one or more generic anti-inflammatory agents or immunomodulatory agents. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Applicant argues that no undue experimentation is required to make the chemically modified EPO for use in the claimed methods (Remarks, p. 16, fifth paragraph). Applicant argues that the "as-filed" specification teaches that "tissue protective cytokines" include erythropoietin (hereinafter EPO) molecules that have been altered. Applicant argues that the modified EPOs could be made and used by a person of skill in the art without undue experimentation (Remarks, p. 16, last two paragraphs). Applicant's argument has been fully considered, but it is not persuasive.

Page 4 of the specification, paragraph 11 states that "tissue protective cytokines" include EPO, but EPO is the only species of tissue protective cytokine taught in the specification. Although claims 8-10, 13-16, 43-46, and 54 encompass EPO, as a tissue protective cytokine, the claims do not recite EPO as a claim limitation. Thus, although EPO is set forth in the specification as an example of a tissue protective cytokine, the claims read on any generic tissue protective cytokine, without further defining the structure or biological function of the cytokine. The term "tissue protective" is also not clearly set forth in the specification because a tissue protective cytokine may encompass cytokines that are protective against infection, for example, but otherwise generate pro-inflammatory responses.

The example of EPO as a member of the genus of tissue protective cytokines is not sufficient to teach one of skill in the art how to make and use the genus of generic tissue protective cytokines, as claimed. The generic genus of tissue protective cytokines in claims 8-10, 13-16, 43-46, and 54 does not adequately correspond to the scope of the subject matter taught in the specification and amounts to nothing more than an invitation to experiment. The scope of the claims includes numerous structurally different amino acid molecules, and the genus is highly variable because a significant degree of structural variation is permitted. Structural features that could distinguish the instantly claimed modified erythropoietin molecules in the genus from other molecules in the amino acid class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Accordingly, there is no means by which the artisan, given any of these cytokine molecules, would know whether it was a member of the genus that could be used in the claimed methods. The instant disclosure of the several specific mutein EPO species does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. One of skill in the art would not be able to predict which cytokine was a tissue protective cytokine and whether it could be

used in the claimed method without undue experimentation. The exemplification of EPO as one species of tissue protective cytokine does not remedy this deficiency in scope.

Further, it is also noted that claim 8, for example, recites that "one or more" anti-inflammatory agents or immunomodulatory agents are to be administered with the tissue protective cytokine. However, the only in vivo working example in the specification (Example 12, pp. 113-114) discloses administration of commercially available EPO (sold as PROCRIT) and dexamethasone. Thus, one immunomodulatory agent is disclosed as being administered with EPO (which is the only tissue protective cytokine taught in the specification), but the specification does not teach the co-administration of more than one anti-inflammatory or immunomodulatory agent.

New claim 54 is rejected along with claims 8-10, 13-16, 43-46, because EPO is the only tissue protective cytokine taught in the specification. The EPO exemplified in the specification (Example 12, pp. 113-114) is commercially available EPO (sold as PROCRIT). However, this EPO is erythropoietic. There are no examples of non-erythrypoietic generic tissue protective cytokines in the specification. If Applicant is referring to a specific modified EPO variant that lacks erythropoietic activity then claim 54 should be amended to so recite.

(Part II)

13. Claims 11-12 and 17-42, remain rejected and new claims 53 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling in the art for a method of treating inflammation in a mammal comprising administering recombinant Epoetin Alpha in an isotonic sodium chloride solution with IFN-β, does not reasonably provide enablement for a method of treating inflammation in a mammal comprising administering EPO or a structurally modified EPO in a pharmaceutically acceptable carrier and one or more generic anti-inflammatory agents or immunomodulatory agents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The nature of the invention is drawn to a method of treating inflammation in a mammal by administering erythropoietin or an erythropoietin derivative or analog and a pharmaceutically acceptable carrier and administering to the mammal one or more anti-inflammatory agents or immunomodulatory agents.

Applicant argues that person of ordinary skill in the art would readily be able to ascertain the structure of the claimed modified EPO molecules by routine chemical modification (Remarks, p. 16, last paragraph to p. 17, first paragraph). Applicant also argues that specific examples for the sites of chemical

modification are provided "e.g. p. 14, lines 10-23 and include e.g. arginine residues, lysine residues, tyrosine residues, glutamic acid residues and tryptophan residues" (Remarks, p. 17, paragraph 2). Applicant also argues that additional examples of sites for modification are detailed "e.g. from p. 30 line 21 to page 38, line 9" (Remarks p. 17, paragraph 2). Applicant argues that examples of methods for chemically modifying EPO such as "guanidation, amidination, carbamylation (carbamoylation), trinitrophenylation, acetylation, succinylation, nitration, among others are provided at p. 29, lines 11-21." Applicant also states that examples of these modifications and others are set forth at "e.g. p. 32, line 21 to p. 38, line 9. Applicant also states that specific desialyation methods are set forth at p. 30, line 21 to p. 31, line 6 (Remarks, p. 17, third paragraph). Applicant also argues that methods for obtaining the required chemical modifications were well-known in the art and cites the book, *Chemical Reagents for Proteins Modification*, 1991 (Remarks, p. 17, last paragraph).

Applicant argues that examples of compound groups of chemically modified EPOs include "e.g. carbaymlated EPOs, succinylated EPOs, acetylated EPOs, biotinylated EPOs, iodinated EPOs, and carboxymethyllysyl EPOs are provided e.g. at p. 39, line 1 to p. 40, line 21" (Remarks, p. 18, first paragraph). Applicant argues that other methods of chemically modifying EPO were also known in the art at the time the application was filed and cites WO 94/24160. Applicant argues that one of skill in the art could use the activity assays described by WO 94/24160 to test particular chemically modified EPOs for suitability for use in the present invention (Remarks, p. 18, second paragraph). Applicant also argues that no undue experimentation would be required to identify suitable chemically modified EPOs for use in the claimed methods (Remarks p. 18, last paragraph). Applicant cites *In re Angstadt* (CCPA 1976) for the proposition that the unpredictability of the results of an experiment is not a basis to conclude that the amount of experimentation is undue (Remarks, p. 18, last paragraph to p. 19, first paragraph). Applicant argues that the specification provides results from in vivo and in vitro studies that demonstrate that one of skill in the art could use an assay to test whether a particular chemically modified EPO has an anti-inflammatory effect and cites Example 12, pp. 110-115, as support (Remarks, p. 19, first paragraph).

Applicant argues that assays for anti-inflammatory effects were well known in the art at the time the application was filed (Remarks, p. 19, second paragraph). Applicant argues that simply because the outcome of a specific assay for each modified EPO may not be known in advance does not make the claimed methods non-enabled since unpredictability of an experiment is not a basis to conclude that the amount of experimentation is undue, citing *In re Angstadt* (Remarks, p. 19, last paragraph).

Applicant argues that evidence of the anti-inflammatory activity of carbamylated EPO and asialyated EPO were known in the art and cites the Savino reference for support (Remarks, p. 20, first two

paragraphs). Applicant argues that the Cuzzoncrea et al., reference demonstrates that EPO exerts an anti-inflammatory effect in a collagen-induced arthritis model in mice (Remarks, p. 20, third paragraph). Applicant argues that the Diem et al., reference (2005) demonstrates that the combined administration of EPO and an anti-inflammatory have synergistic effects (Remarks, p. 20, last two paragraphs to p. 21, first two paragraphs). Applicant argues that the later-published Diem et al., reference supports the demonstration of a synergistic effect of the instantly claimed therapy (Remarks, p. 21, third paragraph). Applicant's arguments have been fully considered, but they are not persuasive.

Regarding Applicant's argument that specific examples for the sites of chemical modification are provided "e.g. p. 14, lines 10-23 and include e.g. arginine residues, lysine residues, tyrosine residues, glutamic acid residues and tryptophan residues" (Remarks, p. 17, paragraph 2). The examiner agrees that the specification recites general information on the generic modifications of EPO, including amino acid sites to modify by "at least one modification" (compare claim 11) (specification p. 14, paragraph 31). The examiner also agrees that a general knowledge of protein modification is also known in the art. However, the specification does not state which of this recited list of amino acids can be modified such that the resulting modified protein still retain function. Modifications of amino acid residues may include addition, deletion, substitution, truncation, or chemical modification. The generic recitation in the specification at page 14, paragraph 31, and the generic claim language (see especially claim 11) of "one or more modified [insert recited residue]…" is not sufficient guidance to give a person of skill in the art so that they would know which sites could be modified, the manner in which they could be modified, and still retain biological function. It is also important to clearly establish that the art of record (see Office Action of 28 March 2007) specifically states that even single amino acid modifications of proteins, especially cytokines, affects protein function. In the instant case, Applicant has simply not provided sufficient guidance to enable a person of skill in the art to make and use the genus of modified EPO variants with "one or more" modifications from the list of amino acid residues. The functional results of any given "modification" are not predictable.

To *a priori* counter the examiner's argument, Applicant cites In re Angstadt and Griffin, 190 USPQ 214 (CCPA 1976) for the proposition that the unpredictability of the results of an experiment is not a basis to conclude that the amount of experimentation is undue (Remarks, p. 18, last paragraph to p. 19, first paragraph). Applicant also argues that simply because the outcome of a specific assay for each modified EPO may not be known in advance does not make the claimed methods non-enabled since unpredictability of an experiment is not a basis to conclude that the amount of experimentation is undue,

citing *In re Angstadt* (Remarks, p. 19, last paragraph). Applicant's reliance on Angstadt is not entirely well-founded.

Angstadt stands for the proposition that the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). The question before the Angstadt court was whether in an unpredictable art, section 112 requires disclosure of a test with *every* species covered by a claim. The court's answer was decidedly no. The court stated that "[h]aving decided that appellants are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art such as the present record presents, each case must be determined on its own facts." (In re Angstadt, at 218). The Angstadt court stated that "we have no basis for concluding that persons skilled in this art, armed with the specification and its 40 working examples, would not easily be able to determine which catalyst complexes within the scope of the claims work to produce hydroperoxides and which do not. Since appellants have supplied the list of catalysts and have taught how to make and how to use them, we believe that the experimentation required to determine which catalysts will produce hydroperoxides would not be undue and certainly would not "require ingenuity beyond that to be expected of one of ordinary skill in the art," Fields v. Conover, 58 CCPA 1366, 1372, 443 F.2d 1386, 1390-91, 170 USPQ 276, 279 (1971)) (In re Angstadt, at 218) [emphasis added].

Angstadt is entirely distinguishable on its facts from the instant case. In Angstadt, the structure for the catalyst was know to those of skill in the art or could be readily determined from a finite list of possibilities, even if the function of the catalyst was in question. The appellant had set forth 40 working examples and the court found that one of skill in the art would be required to conduct merely routine experimentation, given the sufficient guidance set forth in the specification. The court found the disclosure in Angstadt sufficient enough that one of skill in the art would not need to conduct undue experimentation and that conducting such experimentation would not require any ingenuity beyond that of one of ordinary skill in the art. That is not the case with the instant disclosure.

The instant disclosure does not provide sufficient structure for the modified EPO variants. Claim 11(iii), for example, states that the modified EPO moiety has "a reduced carbohydrate content" but no guidance is provided in the specification such that the "reduced carbohydrate" content may be distinguished by any measurable means. It is well known that the addition of carbohydrates are post-translational modifications. A recombinant EPO could be produced in a cell lacking a any given

carbohydrate transferase or sugars can be withheld from a medium during the recombinant production cycle, and EPO variants with decreased carbohydrate structures can be produced. There are approximately 60 known sugar moieties and tens-of-thousands of combinations of complex carbohydrate formations that are possible for any given protein. Not only is the control of post-translational sugar modifications highly unpredictable, but Applicant has not sufficiently addressed how or when to modify the carbohydrate content in the specification. For example, Franze et al., US Patent 6,673,575 (6 January 2004, benefit to 5 September 2000) teach a method of producing recombinant (EPO) by altering the composition of the medium or the conditions of metabolism to effect changes to the degree of glycosylation (p. 4, last paragraph to page 5; column 2, lines 58-63). The sugars to be added to the medium are taught as fructose, mannose, or combinations of glucose and/or mannose (p. 5, third paragraph; column 3, lines 5-9). Total concentration of all sugars during fermentation are in the range of 0.1 to 10 g/L in the culture medium (p. 5, third paragraph, line 22; column 3, lines 15-16). Nutrients added that effect sugar metabolism, including the essential amino acid, glutamine are taught at p. 6, line 23; column 5, line 50). Nutrient solution containing a mass ratio of glutamine to sugars is taught at p. 7, third paragraph; column 4, lines 10-17). Figure 1 shows the dependence of the relative proportion of individual EPO isoforms on the carbohydrates added to the culture medium. Example 3 (p. 12; column 6) teaches a method of determining the proportions of biantennary, triantennary, and tetraantennary carbohydrate structures from CHO cells (p. 12, line 30; column 6, line 64). Example 5 (p. 15; column 8) teaches the steps of controlled feeding including periodically calculating the glutamine concentration and consumption (p. 16; lines 21-22; column 8, lines 55-57) (claims 1, 5-8, 14, 17-24). Table 1 (p. 17; column 9) shows a comparison of the distribution of EPO isoforms fed with different nutrient solutions containing different kinds of sugars (claims 1, 5-6, 8, 9, 12, 16, 17-19). Example 7 (p. 19; column 10) teaches the isoform distribution of EPO glycosylation caused by differences in the feeding of monosaccharides mannose and galactose (p. 20, last paragraph; column 10, lines 57-66). Table 3 (p. 21, column 11) shows the different percentages of biantennary, triantennary, and tetraantennary carbohydrate structures from CHO cells. In the instant case, there is no guidance in the specification about which sugars (other than sialic acid) to modify (compare claim 11(ii)), there is no guidance as to which cell types the EPO variant should be produced in, there are no ratios of sugars to essential amino acids that affect sugar metabolism, such as glutamine. No steps of controlled feeding are taught. In other words, the instant specification invites one of skill in the art to experiment to determine these parameters, but they are not taught. It is also noted, that the specific example of modified EPOs taught by the '575 patent contained very different isoforms within the same batch and from batch to batch because of the extreme

difficulty of controling the post-translational modification of sugars (see column 10, Example 7, especially at lines 57-65).

Regarding claim 11(i), (ii), and (iii), Fukada et al., (Blood. 1989 Jan;73(1):84-9, Abstract Only) (previously cited in the Office Action of 28 March 2007), teach that sialic acid of recombinant erythropoietin is necessary for EPO to circulate stably. Fukada et al., also teach that glycoproteins with more than three lactosyaminyl repeat units may be cleared by the galactose binding protein of hepatocytes (abstract). Fukada et al., clearly demonstrate that not all forms of recombinantly produced EPO are biologically functional. Because the lack of biological function is directly correlated with structural modification of EPO, as demonstrated by Fukada et al., and Satake et al., (discussed below), it would require significant undue experimentation to make Applicant's claimed variants set forth in claims 11-12 and 17-42 and test the same for activity. The biological function of the broad genus of EPO variants cannot be predictably ascertained from the limited disclosure in the specification or from what is known in the art because the art teaches that the structure of the EPO variants is critical to whether the modified protein is biologically functional. Because of this correlation, it would require undue experimentation for a person of skill in the art to make the large genus of claimed EPO variants and test the same for activity. As such, the teachings in the instant specification and the art do not reasonably correlate with the scope of the instant claims.

Similarly, claim 11 recites a list of 6 kinds of amino acid residues that may be modified in the form of "one or more." The native sequence of EPO is known, but one of skill in the art would not know where to begin to start "modifying" each of the one or more amino acid residues and test the same for activity. Claim 11 (xi) recites that one or more amino groups are removed, but Applicant does not teach which amino group or how the removal of the amino group will affect the solubility of the protein. Claim 11 (xii) recites that an opening of at least one of the cysteine [note that cysteine is misspelled in claim 11 (xii)] linkages. An open cysteine linkage would likely create destabilizing effects on tertiary protein structure or create problems with protein aggregation and cross-linking to other proteins with free cysteine residues. Applicant has provided no guidance as to overcome the myriad of structural or functional problems presented by the scope of the claims. Additionally, claim 11, recites a truncated EPO. However, there is no guidance on where to truncate the protein such that it still retains function. Neither the specification nor the claims provide sufficient guidance to teach one of ordinary skill in the art the structure of the EPO variant such that one could carry out mere routine functional studies. Instead, the claims and the specification offer the skilled artisan an invitation to experiment in an unpredictable area of molecular biology, where the art clearly teaches that minor modifications of protein structure cause

critical problems with protein functionality, such that undue experimentation would be required. It is also noted that issues of predictability, are only one of the factors considered under the Wands analysis and that the claims and the specification are examined as a whole, considering all of the Wands factors.

Although working examples are not required, they are considered helpful in determining the predictability and the amount of experimentation necessary to make or use the invention, as claimed. In the present case, Applicant does not provide sufficient working examples of the *in vivo* use of the claimed methods to overcome the evidence of the art (above) stating that structure and function of modified EPO are intimately intertwined and directly correlated. Only one working example of an *in vivo* method is disclosed using commercially available EPO (sold as PROCRIT) co-administered with dexamethasone to EAE rats (Example 12, pp. 112-113). The specification does not provide any working examples of in vivo use of modified EPO administered in conjunction with an anti-inflammatory or an immunomodulatory agent. The lack of working examples in the instant specification directed to modified EPO structure and function, weigh against Applicant's arguments that the modified EPO variants are predictable and that one of skill in the art would not be required to engage in undue experimentation to make and/or use them (see Remarks, pp16-21). Further, Applicant's assertion that the only experimentation required would be routine experimentation in light of the fact that there are no working examples using any form of modified EPO in conjunction with an anti-inflammatory or immunomodulatory agent, as claimed. Instead of using modified EPO variants in the one in vivo method (Example 12), Applicant chose to use commercially available recombinant EPO, sold as PROCRIT).

With regard to Applicant's argument that examples of methods for chemically modifying EPO such as "guanidation, amidination, carbamylation(carbamoylation), trinitrophenylation, acetylation, succinylation, nitration, among others are provided at p. 29, lines 11-21" and that examples of these modifications and others are set forth at "e.g. p. 32, line 21 to p. 38, line 9. (Remarks, p. 17, third paragraph). The instant claims are not supported by a fully enabling disclosure commensurate in scope with the claims, as written. Satake et al., (Biochimica et Biophysica Acta. 1990;1038:125-129) (previously cited of record) teach that modification of lysine residues to neutral or negative charges, such as in acetylation, trinitrophenylation, carbamylation or succinylation cause a significant loss of recombinant human erythropoietin activity. Satake *et al.* also teach that the biological activity of recombinant human erythropoietin (EPO) is sensitive to chemical modifications of lysine residues (abstract and page 127, paragraphs two and three, Table 1 and page 128, Discussion). The instant specification is silent regarding the biological activity of EPO having at least one or more modified lysine residues, for instance neutral or negative charges to lysine residues, which are as effective as unmodified

EPO. The instant specification does not teach the administration of the claimed lysine-modified EPO to mammals either alone or in combination with an anti-inflammatory or an immunomodulatory agent. The specification need not contain an example if the claimed invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lack of working examples, however is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. In this case, the art is unpredictable based on the evidence provided. One skilled in the art cannot readily anticipate the *in vivo* biological effect of the claimed invention on a mammalian subject.

Regarding Applicant's that the specification provides results from *in vivo* and *in vitro* studies that demonstrate that one of skill in the art could use an assay to test whether a particular chemically modified EPO has an anti-inflammatory effect and cites Example 12, pp. 110-115, as support (Remarks, p. 19, first paragraph). Applicant's Example 12 shows the administration of commercially available recombinant EPO (PROCRIT) co-administered with dexamethasone in EAE rats. Example 12 notes that the EPO delayed the onset of disease in a dose dependent fashion, but did not delay the time to greatest severity (paragraph 319, p. 113). Paragraph 320 of Example 12 also states that no relapse was seen after withdrawal of EPO, such as those seen after withdrawal of dexamethasone. However, it is unclear from paragraph 320 whether there was any relapse after withdrawal of concominatly administered EPO and dexamethasone. Paragraph 320 suggests that the withdrawal symptoms were observed when one or the other drug was used individually, but it is silent as to whether there was any relapse when the drugs were used together. In any case, Example 12 does not show synergistic results of co-administration of EPO and the immunomodulatory drug, dexamethasone. At most, it may tend to show that EPO acts in an unknown manner to decrease the symptoms of a relapse to a subclinical level, but no data are provided that tend to show synergistic results.

Applicant argues that assays for anti-inflammatory effects were well known in the art at the time the application was filed (Remarks, p. 19, second paragraph). Applicant argues that evidence of the anti-inflammatory activity of carbamylated EPO and asialyated EPO were known in the art and cites the Savino reference for support (Remarks, p. 20, first two paragraphs). Applicant argues that the Cuzzoncrea et al., reference demonstrates that EPO exerts an anti-inflammatory effect in a collagen-induced arthritis model in mice (Remarks, p. 20, third paragraph). Applicant argues that the Diem et al., reference (2005) demonstrates that the combined administration of EPO and an anti-inflammatory have synergistic effects (Remarks, p. 20, last two paragraphs to p. 21, first two paragraphs). Applicant argues that the later-published Diem et al., reference supports the demonstration of a synergistic effect of the

instantly claimed therapy (Remarks, p. 21, third paragraph). Applicant's arguments have been fully considered, but they are not persuasive.

With regard to the Cuzzoncrea et al., reference, it is non-analogous art. Cuzzoncrea et al., discuss the co-administration of EPO with CII (collagen type II), which is a proteinaceous agent (compare claim 10), but it induced rheumatoid arthritis in mice. It is unclear whether Applicant is expanding the scope of the claims to encompass "immunomodulatory" agents that actually cause disease. If this is the case, then the combination of an immunomodulatory agent that induces disease runs counter to the recited use of the method "for treating inflammation in a mammal." Cuzzoncrea et al., do not teach the administration of EPO and an anti-inflammatory or an immunomodulatory agent that does not cause disease.

With regard to Savino et al., it is also non-analogous art. Savino et al., investigated carbamylated EPO and asialylated EPO but not in conjunction with an anti-inflammatory or immunomodulatory drug.

With regard to the Diem et al., reference, the authors state that one of the aims of their study was to test the hypothesis that MPred and EPO would have synergistic effects when co-administered (p. 376, last paragraph of the introduction). However, if one reads farther into the paper, one will see that the authors state that "late, short-duration EPO was beneficial when treatment was combined with high-dose MPred therapy....although beneficial effects of MPred on axon counts can also be seen if MPred was given as monotherapy" (p. 383, column 2, last paragraph to p. 384, first paragraph, and lines 4-6 of paragraph 2, column 1). Diem et al., suspect that the suppressing effect of EPO on the production of proinflammatory cytokines during early development of EAE synergistically enhances MPred-induced tissue protection, but there is insufficient data in their paper to support this assertion (p. 384, column 1, last sentence of second paragraph). Evidence of a greater than expected result may be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to establish synergy because such an effect can either be expected or unexpected. In the case of Diem et al., it is unclear whether the effect of the combination of EPO and MPred was merely the actions of each of the drugs additively, but not synergistically. In support of this argument, Diem et al., also note that the administration of EPO as an exogenous neurotrophin-like substance may compensate for the lack of endogenous neurotrophic factor support resulting from anti-inflammatory treatment of EAE or multiple sclerosis (p. 384, column 2, end of first paragraph).

Of critical importance to the scope of enablement argument, is Applicant's own post filing work. Not only is it an admission of the lack of predictability of the breadth of the claimed methods, but it also

specifically disavows the independent claims herein and says not only that they will not work, but should be avoided. Gorio et al., (PNAS USA. 2005 Nov 8;102(45):16379-84. Epub 2005 Oct 31) teaches that methylprednisolone sodium succinate (MPSS) neutralizes the beneficial effects of erythropoietin in experimental spinal cord injury. The suppression of proinflammatory cytokines alone does not necessarily prevent secondary injury and **glucocorticoids should not be coadministered** in clinical trials evaluating the use of EPO for treatment of spinal cord injury. Using a rat model of contusive SCI, the authors compared the effects of EPO [500-5,000 units/kg of body weight (kg-bw)] with MPSS (30 mg/kg-bw) for proinflammatory cytokine production, histological damage, and motor function at 1 month after a compression injury. Although high-dose EPO and MPSS suppressed proinflammatory cytokines within the injured spinal cord, only EPO was associated with reduced microglial infiltration, attenuated scar formation, and sustained neurological improvement. **"Unexpectedly, coadministration of MPSS antagonized the protective effects of EPO, even though the EPO receptor was up-regulated normally after injury."** [Emphasis added.] Gioro et al., is not only evidence of the lack of predictability of co-administering EPO with an immunomodulatory agent or anti-inflammatory agent, such as a glucocorticoid, but it is also evidence that the claims, as written, are not workable and cannot be used by one of skill in the art to treat inflammation in a mammal.

It is also noted that at least one of the co-inventors is a co-author in the Gioro et al., reference. Further, in looking for potentially synergistic effects, not only did Gorio et al., not find any synergistic effects, they found effects that render the claimed combination **deleterious** for use when co-administered to reduce inflammation.

As previously stated in the Office Action of 28 March 2007, the level of skill of those in the art is high due, in part, to the unpredictability of the biological function of proteins with altered amino acid or glycosylation structures. The assertion that the disclosed erythropoietin variants have biological activities similar to known recombinant Epoetin alfa cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities.

It is also noted that other art references teach concurrent administration of recombinant EPO (usually as Epoetin Alfa, sold as PROCRIT) with low dose specific agents to treat inflammatory conditions. For example, Kitajima et al., (Rinsho Ketsueki. 1994 Jul. 35(7):694-8, Abstract only) (previously cited of record), teach a method of treating inflammation using recombinant EPO, Cepharanthin, and low dose prednisone and Schiffl et al., (Eur J Med Res. 1997 Mar 24;2(3):97-100, Abstract only) teach concurrent administration of EPO and the non-steroidal anti-inflammatory drug

indomethacin for treatment of end-stage renal disease. These references are distinguishable from the instant claims because they use recombinant EPO, but not modified EPO protein variants. These references also use very specific coadministered compositions, for example, low dose prednisone, and indomethacin. Although the art teaches the successful co-administration of these compounds, there is no support in the art for co-administering the breadth of the claimed modified EPO variants with the claimed generic genera of anti-inflammatory or immunomodulatory agents. The breadth of Applicant's claims render the claims unpredictable and require undue experimentation for one of skill in the art to make or use the invention as claimed.

It is also noted that the specification states that the present invention relates to "tissue protective cytokines" generated by the chemical modification of erythropoietin and their uses on erythropoietin-responsive and associated cells (p. 2, paragraph 6). However, the specification does not teach erythropoietin as a tissue protective cytokine, but rather, teaches erythropoietin as an inducer of tissue protective cytokines (see p. 2, paragraph 6).

New claims 53 and 54 are also rejected along with claims 8-46 for the reasons set forth above. EPO is the only tissue protective cytokine taught in the specification. The EPO exemplified in the specification (Example 12, pp. 113-114) is commercially available EPO (sold as PROCRIT). However, this EPO is erythropoietic. There are no working examples of administering a non-erythrypoietic generic tissue protective cytokine and an anti-inflammatory or immunomodulatory agent in the art or the specification. If Applicant is referring to a specific modified EPO variant that lacks erythropoietic activity then claim 54 should be amended to so recite. Whether any generic modified EPO variant would lack erythropoietic activity is entirely unpredictable. Additionally, the question of whether a modified EPO variant is non-erythropoietic calls into question the activity assays that Applicant's argued (see above) were routine in the art. Applicant has not provided any guidance to show one of ordinary skill in the art how they can make or test a modified EPO variant for activity if the modified EPO variant is no longer required to be erythropoietic. See, for example, Remarks p. 18, second paragraph, where Applicant states "[i]n terms of biological function, EPO has been recognized as a hematopoietic cytokine that regulates the process of red blood cell production, known as erythropoiesis." If the modified EPO variants do not have a definite structure and they do not have a definite, testable function, it would require undue experimentation to make and use the claimed invention and doing so would be entirely unpredictable.

Due to the large quantity of experimentation necessary to generate the modified EPO variants and derivatives recited in the claims and screen same for activity for use in the claimed method, the lack of

direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the lack of working examples directed to same, the complex nature of the invention and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

14. Claims 8-10, 13-16, 43-46 remain rejected and claim 54 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant argues that the person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing (Remarks, p. 22, first paragraph). Applicant argues that the Written Description Guidelines and Capon v. Escher do not require Applicant to disclose in detail what is well known in the art (Remarks, p. 22, last paragraph to p. 23, first paragraph). Applicant argues that the genus of mammals is well known in the art (Remarks, p. 23, first full paragraph). Applicant argues that the genus of tissue protective cytokines is described (e.g. at p. 4, paragraph 11) of the specification (Remarks p. 23, second full paragraph). Applicant argues that anti-inflammatory agents and immunomodulatory agents were well known in the art (Remarks, p. 23, third full paragraph). Applicant argues that "disease conditions" or "trauma" are also conventional and known and therefore need not be recited in the application. Applicant's arguments have been fully considered, but they are not persuasive.

The claims, as written, are drawn to a method for treating inflammation in a mammal comprising responsive cells by administering to a mammal a tissue protective cytokine and a pharmaceutically acceptable carrier and an effective amount of one or more anti-inflammatory agents or immunomodulatory agents.

Page 4 of the specification, paragraph 11 states that "tissue protective cytokines" include EPO, but EPO is the only species of tissue protective cytokine taught in the specification. Although claims 8-10, 13-16, 43-46, and 54 encompass EPO, as a tissue protective cytokine, the claims do not recite EPO as a claim limitation. Thus, although EPO is set forth in the specification as an example of a tissue

protective cytokine, the claims read on any generic tissue protective cytokine, without further defining the structure or biological function of the cytokine. The term "tissue protective" is also not clearly set forth in the specification because a tissue protective cytokine may encompass cytokines that are protective against infection, for example, but otherwise generate pro-inflammatory responses.
The example of EPO as a member of the genus of tissue protective cytokines is not sufficient to describe the genus of generic tissue protective cytokines. The generic genus of tissue protective cytokines in claims 8-10, 13-16, 43-46, and 54 does not adequately correspond to the scope of the subject matter disclosed in the specification. The genus of generic tissue protective cytokines includes numerous structurally different polypeptides, and the genus is highly variable because a significant degree of structural variation is permitted. Structural features that could distinguish the instantly claimed modified erythropoietin molecules in the genus from other molecules of the genus are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because a specific disclosure is needed. The instant disclosure of the several specific mutein EPO species does not provide an adequate description of the claimed genus of tissue protective cytokines, which encompass a substantial variety of subgenera. The exemplification of EPO as one species of tissue protective cytokine does not remedy this deficiency in the disclosure. While "examples explicitly covering the full scope of the claim language" typically will not be required, a sufficient number of representative species must be included to "demonstrate that the patentee possessed the full scope of the [claimed] invention." Lizardtech v. Earth Resource Mapping, Inc., 424 F.3d 1336, 1345, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005).

New claim 54 is rejected along with claims 8-10, 13-16, 43-46 because EPO is the only tissue protective cytokine described in the specification. The EPO exemplified in the specification (Example 12, pp. 113-114) is commercially available EPO (sold as PROCRIT). However, this EPO is erythropoietic. There are no descriptions in the specification of non-erythyropoietic generic tissue protective cytokines administered to mammals with anti-inflammatory or immunomodulatory agents for the treatment of inflammation.

With regard to Applicant's reliance the Written Description guidelines, "[c]ompliance with the written description requirement is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed" Vas-Cath Inc. v. Mahurhar, 935 F.3d at 1563, 19 USPQ2d at 1117). While the Written Description Guidelines and hypothetical examples in the Synopsis can be helpful in understanding how to apply the relevant law, as it existed in 2001 when the Guidelines were adopted, they do not create a rigid test.

In the absence of sufficient recitation of distinguishing characteristics of tissue protective cytokines the specification does not provide adequate written description of the claimed genus, beyond the one species of EPO and variants thereof. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the claimed genus. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features (see, Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004); accord Ex Parte Kubin, 2007-0819, BPAI 31 May 2007, opinion at p. 16, paragraph 1).

Conclusion

NO CLAIM IS ALLOWED.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERIE M. WOODWARD whose telephone number is (571)272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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